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Hepatocellular Carcinoma: Challenges in Indian Scenario

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ABSTRACT

Hepatocellular carcinoma (HCC), a leading solid organ malignancy is on the rise across the world, including India. Its incidence has almost tripled in the last 30 years and it is among the fastest growing malignancy in the USA. It is the third most frequent cause of death from cancer and the eighth most commonly occurring cancer in the world. A disease of multifactorial etiology, HCC poses many challenges. It demands multidisciplinary care involving diagnostic, medical and surgical inputs. A lot of research is ongoing in terms of attempts to improve its treatment and results thereof. Identification of some of the causative factors has resulted in efforts towards its primary prevention as well. Universal immunization against Hepatitis B virus is one such effort in this direction. Identification of role of various molecular pathways is leading to targeted drug developments offering personalized treatment to concerned patients. The authors have been involved in the diagnosis and management of this important liver cancer. This article summarizes the various challenges encountered in the diagnosis and management of HCC in India.

Keywords: Hepatocellular carcinoma (HCC), risk factors, staging of HCC, liver transplantation, transarterial chemoembolisation (TACE), transareterial radioembolisation (TARE), targetted therapy, sorafenib.

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer related deaths worldwide (1). Significant advances have been made in our knowledge regarding the risk factors and pathogenic mechanisms of this tumor. However, the burden of this tumor continues to rise worldwide, and it is among the leading cause of death among patients with cirrhosis. The most common risk factors for HCC that have been identified in the Indian setting are viral Hepatitis B and C, alcoholic cirrhosis, non-alcoholic fatty liver disease (NAFLD) and aflatoxins (2). HCC develops in the setting of cirrhosis in 80-90%, which itself is a pre-neoplastic state. The treatment of HCC depends not only on the tumor characteristics itself, but also on the presence and stage of underlying cirrhosis. The development of preclinical models have shown the importance of molecular signaling pathways and angiogenesis in the pathogenesis of HCC (3). This has led to the use of molecular targeted therapy with agents such as sorafenib, a multikinase inhibitor, in the treatment of HCC (3, 4). Despite only a modest benefit in the overall survival with the use of sorafenib, its use in HCC has been an important milestone that has opened up the options of using newer molecular targeted therapies.

Epidemiology

HCC is the most frequent cause of all liver cancers and constitutes 90% of cancers of liver globally. The prevalence of HCC available in autopsy data of Dhir and Mohandas (Table 1) revealed that 0.2–1.9% of autopsy cases

Table 1 : Autopsy Date on HCC in India (5)

Place	Autopsies (No.)	HCC (%)
India		
Mumbai	**6000**	**0.2**
Mumbai	**4000**	**0.2**
Agra	**1234**	**0.7**
Guntur	**629**	**1.1**
Andhra Pradesh	**2789**	**1.6**
Chennai	**1218**	**1.9**

had HCC with a higher prevalence in southeastern states of India (5). The incidence of HCC in cirrhotics in India is 1.6% per year. The male:female ratio for HCC in India is 4:1. The age of presentation varies from 40 to 70 years. The age standardized mortality rate for HCC in India for men is 6.8/100,000 and for women is 5.1/100,000. The available data indicate that the age adjusted incidence rate of HCC in India for men ranges from 0.7 to 7.5 and for women 0.2 to 2.2 per 100,000 population per year, the highest being reported from Sikkim and Mizoram (6).

Patients with cirrhosis of liver of any cause are at a high risk for developing HCC, and almost 80% of HCC cases reported globally have underlying cirrhosis. Reports from tertiary care centres in India on HCC indicate that 70–97% of patients with HCC at the time of diagnosis had underlying cirrhosis of liver (7, 8). Long term cohort follow-up studies from Europe and USA indicate that annual frequency of HCC in HBV-cirrhosis, HCV-cirrhosis and alcohol-induced cirrhosis have been 2.2%, 3.8% and 1.7%, respectively (9, 10).

In a prospective observational study, patients with Child's A and Child's B cirrhosis without HCC at enrollment (n = 194) were followed up for a median duration of 44 months with ultrasonography and AFP at 6 month interval, and triphasic CT annually. During the follow-up, nine cases of HCC (all males) were detected with an annual incidence rate of 1.6% (95% CI—0.07–3) (11). The authors concluded that incidence rate of HCC among Indian patient with cirrhosis is intermediate between high rates in Japan for East and European countries (11). However, unpublished data from various tertiary care centres suggest that the incidence of HCC is increasing in India.

Risk Factors for Hepatocellular Carcinoma

In India HBV and HCV infection, overt cirrhosis of the liver and alcohol intake are the predominant risk factors for the development of HCC (12). The relative risk of developing HCC in Indian patients with chronic HBsAg infection was estimated to be 17.89 from various studies (13). Hepatitis B virus is known to cause genomic integration in the liver tissue resulting in chromosomal deletions and in turn metaplasia. The transactivating potential of HBx protein

can alter the p53 tumor suppressor gene (14-16). HCV-related carcinogenesis is possibly related to chronic inflammation and cirrhosis (17). Nalpas *et al* (18) reported a positive association between HCC and consumption of alcohol in which alcohol works as a cofactor for hepatotoxins and hepatitis viruses.

Alcohol acts as a cocarcinogen in the pathogenesis of HCC, by inducing cirrhosis, and by increasing the risk of viral infections (HBV and HCV). It also has as its effects on P450 mixed function oxidase system, thus causing enhanced activation of chemical carcinogens (15). Diabetic patients with NAFLD are at increased risk of advanced liver disease, cirrhosis and HCC. Diabetes and obesity can cause hepatic inflammation which leads to oxidative stress and lipid peroxidation of the phospholipid constituents of hepatocyte and intracellular membranes, resulting in hepatocyte injury and necrosis, and subsequently HCC (19). Diabetes mellitus was shown to increase the risk of primary liver cancers in the presence of other risk factors such as hepatitis C or B, or alcoholic cirrhosis (20).

Aflatoxins, a secondary metabolite produced by *Aspergillus flavusital* and *Aspergillus parasiticus*, are potent human carcinogens implicated in HCC (21) and also it is proved to have a significant association with HCC in India. Approximately about one quarter of HCC cases diagnosed in India do not have any known predisposing risk factors.

Tumor Staging

Tumor staging, the cornerstone in deciding the management approach in HCC, involves assessment of the extent of the disease, the presence and severity of underlying cirrhosis, its complications, and the performance status of the patient. Several prognostic factors have been identified that correlate with tumor burden and degree of liver dysfunction (22, 23). Several staging symptoms for HCC have been developed such as Barcelona Clinic Liver Cancer (BCLC) (24), Cancer of the Liver Italian Program (CLIP) (25), Groupe d'Etude et de traitement du Carcinome Hepatocellulaire (GRETCH) (26), Tumor-node-metastases system (TNM) (27), Chinese University Prognostic Index (CUPI) (28) and Japanese Integrated System (JIS) (29). Of these, the BCLC staging system is used

most commonly which allows stage-based treatment of HCC. A significant proportion of HCC patients in India are diagnosed at a late stage, which precludes curative treatment options.

Barcelona Clinic Liver Cancer (BCLC) Staging System

The BCLC staging incorporates tumor characteristics, severity of underlying liver disease, performance status, and a recommended treatment algorithm for each stage (Fig. 1). In addition, the BCLC system also provides an estimate of life expectancy based on treatment response (30). It categorizes the patients in to early HCC (stage 0 and A), intermediate stage HCC (stage B), advanced stage HCC (stage C) and end-stage HCC (stage D). Based on tumor stage, the treatment can be either curative or palliative. The curative treatment modalities include surgical resection, local ablative therapies such as radiofrequency ablation (RFA) or percutaneous ethanol injection (PEI), and liver transplantation, whereas the palliative treatment modalities include transarterial chemoembolization (TACE) or radioembolisation (TARE), and molecular targeted therapy with Sorafenib. Those with end-stage HCC

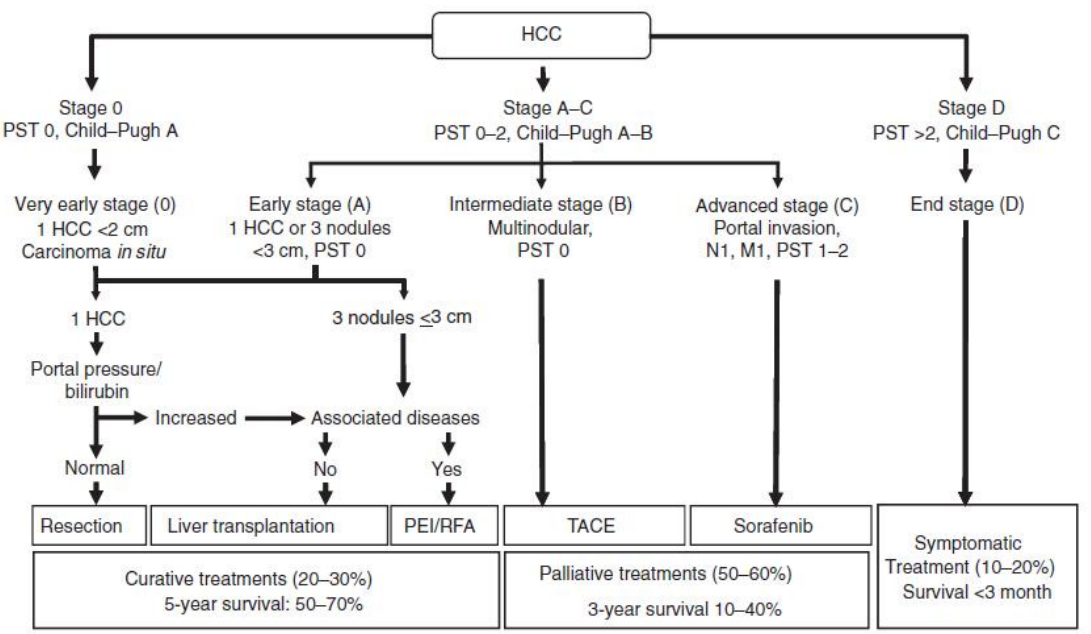

Fig. 1: The Barcelona Clinic Liver Cancer (BCLC) staging classification for the management of hepatocellular carcinoma (Adapted from Ref. 30).

are offered symptomatic treatment only. The therapeutic strategies based on HCC stage are discussed below in details.

Therapeutic Approaches based on HCC Stage

The management of HCC is largely guided by the tumor stage as defined by the BCLC criteria. Majority of HCC cases in India are diagnosed at a late stage that precludes curative treatment options.

Management of Early-Stage HCC (Stages 0 and A)

Early stage HCC can be treated by curative therapies such as surgical resection, local ablation, liver transplantation.

Resection: Patients with early stage HCC with Child's A cirrhosis can be treated with local resection as the risk of hepatic decompensation is low. However, the risk of tumor recurrence in the remnant cirrhotic liver can be as high as 70% at 5 years (31). It is important to evaluate the liver function carefully prior to liver resection so as to avoid post-resection liver decompensation.

Local Ablative Strategies: RFA and PEI are the two most common modes of local tumor ablation. Ablative therapies are useful for patients with small tumors who are poor surgical candidates, either because of impaired liver function or significant co-morbidities (32). RFA is the modality of choice; however, it is significantly more expensive as compared to PEI. RFA is not suitable for tumors in sub-capsular location. Also, it is less effective for tumors that are in close proximity to large blood vessels (due to the 'heat sink' effect that lowers the lethal heat needed for tumor coagulation). As PEI is less expensive, it continues to have its importance in India.

Liver Transplantation: Liver transplantation is often considered as the treatment of choice as it not only removes the tumor, but also removes the cirrhotic liver which itself is in a pre-neoplastic state. The 5-year tumor recurrence rate following transplantation is lower in early stage HCC as compared to resection (10-20% versus 70-80%, respectively). Liver transplantation is now a well established treatment modality in India. Its results in India are at par with the best in the world. Patient selection for liver transplantation is guided by several well described criteria of which "Milan criteria" is the most widely accepted (Table 2). Patients offered transplantation within Milan

Table 2: Criteria for selection of HCC patients for liver transplantation

Conventional Criteria	Country, year (Ref.)	Details	Results
Milan Criteria	Italy, 1996 (33)	Single tumor ⩽5 cm, or ⩽3 tumors none exceeding 3 cm and No vascular invasion and /or extrahepatic spread	5 year survival >70% 5 year tumor recurrence <15%
Extended Criteria			
UCSF Criteria	USA, 2001 (34)	Single tumor ⩽6.5 cm, or ⩽3 lesions none exceeding 4.5 cm with total tumor diameter ⩽8 cm No vascular invasion and /or extrahepatic spread	1 year survival 90% 5 year survival 75.2%
Asan Criteria	Korea, 2008 (35)	Diameter ⩽5 cm Number of lesions ⩽6 No gross vascular invasion	5 year OS 76.3% 5 year recurrence 15%
Hangzhou criteria	China, 2008 (36)	Lesion ⩽8 cm or Lesion ⩾8 cm if AFP ⩽400 and well-differentiated No gross vascular invasion	1 year DFS 83.7% 5 year DFS 62.4% 5 year OS 70.7%
Up to 7 criteria	Italy, 2009 (37)	Sum of the largest tumor diameter in cm and number of tumors ⩽7	1 year recurrence 4% 5 year recurrence 14% 5 year survival 71%

OS = Overall Survival; DFS = Disease Free Survival

criteria have an expected 4-year survival rate of 85% and a recurrence-free survival rate of 92% (33). With greater experience, many centres are extending the Milan criteria, and have adopted the UCSF criteria or beyond (34-37). Many centres in India performing living donor liver transplantation (LDLT) have adopted this strategy as it obviates the donor waiting time and does not interfere with deceased organ sharing, which itself is a scare resource. For patients with decompensated cirrhosis (Child Pugh Class B or C) with HCC who fall within the transplantation criteria, liver transplantation is clearly the treatment of choice. Patients with tumors beyond the accepted criteria are down-staged with bridging therapies such as TACE or RFA, either alone or in combination (38).

Management of Intermediate Stage HCC (Stage B)

Transarterial Chemoembolisation (TACE) : Intermediate stage HCC (stage B) patients typically have large or multifocal tumors, without macrovascular invasion or extrahepatic spread with adequate liver function. These tumors are not amenable to local ablation or curative resection, and are beyond the accepted criteria for liver transplantation. TACE or transarterial embolization (TAE) is the recommended treatment option for these patients. In TACE, various chemotherapeutic agents such as doxorubicin, cisplatin or epirubicin are delivered to the lesion selectively prior to arterial obstruction. Some randomized studies have shown survival benefit following TACE for intermediate stage HCC with an improvement from 10% to 40-50% at 3 years (39, 40). However, a recent meta-analysis which included six trials assessing TACE versus control and three trials assessing TAE versus control did not show a significant survival benefit in patients with unresectable HCC (41).

Besides conventional TACE, another novel strategy to use is drug eluting beads loaded with doxorubicin, also called DEB TACE or Precision TACE. The deformable beads absorb the chemotherapeutic agent, which is then released slowly at the tumor site, with minimal systemic toxicity. Recent trials of TACE with drug eluting beads have shown good response rates with minimal systemic side effects of chemotherapy (42, 43).

Transarterial Radioembolisation (TARE) : TARE is a form of intra-arterial therapy that delivers radiation selectively at the tumor site using yttrium-90 microspheres. These microspheres can be delivered selectively to one or more tumor sites, where they get trapped in the tumor capillary bed. These microspheres selectively induce tumor necrosis by delivering up to 150 Gy of beta radiation, and also by microscopic embolization by obstructing the tumor capillary bed (44). One of the advantages of TARE over TACE is that it can be used in patients with portal vein thrombosis (45).

Management of Advanced Stage HCC (Stage C)

Systemic Therapy for Advanced HCC : Majority of patients with HCC have advanced, unresectable disease at diagnosis. Some of these can be helped by ablative techniques and embolization procedures. However, those with very advanced widespread disease are offered

systemic therapy.

Chemotherapy : HCC is a relatively chemo-resistant tumor, due to expression of multidrug resistance gene protein on the surface of these cancer cells, resulting in active eflux of chemotherapeutic drugs. Some of the chemotherapeutic agents that have shown activity include doxorubicin, cisplatin, fluorouracil, gemcitabine and capecitabine (46-48). These have resulted in response rates of approximately 10% only with no impact on the overall survival. The combination chemotherapy results in improved response rates of about 20%, but has failed to provide any survival advantage.

Chemoimmunotherapy has also been used to treat advanced metastatic HCC. A combination of cisplatin, interferon-alpha, doxorubicin and infusional 5-fluorouracil (PIAF) resulted in response rates of 26%. The median survival was also longer with PIAF regimen than with single drug doxorubicin. However, treatment-related toxicity was also much greater. Chemoimmunotherapy could thus be used only for young patients without cirrhosis and with normal serum bilirubin levels (49).

Targeted Therapy : More recently, targeted therapies have been developed for treatment of various malignancies including HCC. Sorafenib is one such targeted drug approved for treatment of advanced HCC. It is an oral multikinase inhibitor that suppresses tumor cell proliferation and angiogenesis. In a randomized placebo controlled phase III trial (Sorafenib in advanced hepatocellular carcinoma – SHARP study (4), 602 patients with advanced HCC were randomized to receive Sorafenib or best supportive care. The median overall survival was significantly longer in the Sorafenib arm (10.7 months versus 7.9 months in the placebo arm; $p < 0.001$). Approximately 70% of patients in this study had macroscopic vascular invasion, extrahepatic disease or both; and majority had preserved liver function and good performance status.

The Asia Pacific study (50) was another phase III study of Sorafenib that enrolled only Asian patients. In contrast to SHARP study, the patients in Asia Pacific study were more likely to be younger, have HBV-related disease, symptomatic disease and a higher number of tumor sites. The reported median overall survival was 6.5 months in Sorafenib arm versus 4.2 months in the placebo arm. Sorafenib was well

tolerated in both these studies.

These studies suggested that Sorafenib is an effective treatment for patients with advanced HCC. It's efficacy in patient's with Child Pugh class B liver function, appears to be lower than in patients with Child Pugh class A liver functions. A phase II study by Abou-Alfa et al (51), reported lower median overall survival for patients in Child Pugh class B patients (3.2 months compared to 9.5 months in class A patients). Similar worse outcomes have been reported for class B and C patients in many other studies. Based on these reported studies, Sorafenib is considered as category 1

Table 3: Targeted Therapy for HCC: Newer targets

Class	Agents	Phase of development	Outcome/ result
1. Antiangiogenesis	Sunitinib	III (first-line)	failed to demonstrate superiority / non-inferiority to sorafenib
	Brivanib	III (second-line)	failed to demonstrate improved OS in second-line
	Linifanib	III (first-line)	ongoing
	Ramucirumab	III (second-line)	ongoing
	Bevacizumab	II	modest clinical activity as single agent & in combination with erlotinib/chemotherapy
2. Epidermal-Growth Factor Receptor inhibitors	Erlotinib	II	modest activity in single-arm studies
	Gefitinib	II	no convincing anti-tumor activity
	Lapatinib		
	Cetuximab		
3. mTOR inhibitors	Everolimus	I & II	tolerable, efficacious in single-arm studies
	Temsirolimus	III	ongoing
	Sirolimus		
4. c-Met inhibitors	Tivantinib	II	improved time to progression
	Cabazantinib	II	evidence of anti-tumor activity
5. MEK inhibitors	Selumetinib	Multicentre single-arm study	minimal single agent activity
6. Histone deacetylase inhibitor	Belinastat	I	ongoing trials
	Vorinostat		
7. HSP-90 inhibitor	STA-9090	I	ongoing trials

option for selected patients with Child Pugh class A liver function and as category 2A option for patients with class B liver functions.

The recommended target dose of Sorafenib is 400 mg twice daily. In clinical practice, many clinicians adopt a step-up approach, wherein they start patients on 400 mg daily and gradually increase the dose to 800 mg daily as per tolerance. Common adverse effects of Sorafenib include fatigue, anorexia, hand-foot syndrome and diarrhea. It could also be associated with hypertension, laboratory abnormalities (elevations in serum amylase and lipase, hypophosphatemia), etc.

New molecular targets have been identified in HCC and various targeted therapies have been developed. These are in various phases of development and are listed in Table 3 (52-55).

Conclusion

Thus management of this complex disease, HCC continues to be challenging for the treating healthcare professionals on many counts such as:

(a) HCC is a clinically, pathologically, and molecularly a heterogeneous disease.

(b) Its management involves multidisciplinary team approach including the hepatologist, interventional radiologist, surgeon, medical oncologist and pathologist. Hepatologists are crucial to integrated care, because they are the specialists most involved in screening and diagnosis, presurgical and postsurgical resection or liver transplantation, and care of the patients with liver cirrhosis and decompensated liver disease. But such an integrated team of experts is available at very few centres in India.

(c) Latent and asymptomatic presentations in some patients make early detection and treatment very difficult.

(d) Presently available tumor markers have limitations, and there is a need for newer biomarkers to better define the tumor biology and outcome, and choose the optimum treatment.

(e) Screening for HCC is still a matter of considerable controversy.

(f) Few patients are suitable for

surgery on presentation of disease because of advanced disease, age, or co-morbidities.

(g) There is scarcity of liver donors in deceased donor setting, and several centres in India have adopted the living donor liver transplant approach.

(h) Another unique aspect of HCC biology is its recurrence after resection. Even when HCC is successfully treated and cure is achieved, most patients have underlying liver cirrhosis and face a 70% 5-year recurrence risk.

(i) There are little data or RCTs supporting the use of adjuvant therapy.

(j) There is lack of awareness of the disease among the general public, healthcare providers, policy makers, and population at risk.

(k) There is generally poor accessibility to healthcare, and lack of screening programs in large parts of the country.

(l) The number of patients with HCC is rising.

(m) Sorafenib is the only FDA-approved systemic therapy for advanced HCC. However, the outcomes are not uniform for all patients and are far from satisfactory.

(n) The very high cost of treatment and care of patients with HCC, as well as high morbidity and mortality rate are other challenges in India.

The management plan of patients with HCC is affected by the presence of underlying liver disease, the etiology of HCC and its effect on the host liver. The outcome has definitely improved for Indian patients as well with resections, liver transplantation and regional therapies. Over the past decade, there have been active efforts towards drug development to treat such patients. Many molecular targets have been identified and drugs developed. Sorafenib has been approved for advanced HCC based on Phase III trials demonstrating survival benefit. Universal immunization against Hepatitis B virus is an important step towards primary prevention of HCC in India. Active research is ongoing towards refining surgical techniques and identifying molecules for sorafenib failures. As in many other malignancies, we have moved ahead towards personalized treatment in HCC as well.

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Medicalization of Nervous and Emotional Problems

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ABSTRACT

Medicalization is the process of defining non-medical problems in medical terms, usually with the implication that a medical intervention is needed. It has been criticized for re-labeling "normal" human experiences as pathological or medical conditions. Some of the driving engines of medicalization include growth of pharmaceutical industry, advertising, managed care, and biotechnology. In the last few decades, serious concerns have also been raised about medicalization of mental health issues. Diagnosis such as attention-deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD) and sexual disorders are discussed in context of medicalization. Also, role of various stakeholders in dealing with medicalization are discussed.

Keywords: Medicalization, mental health, attention deficit hyperactivity disorder (ADHD), medical marketing, post-traumatic stress disorder (PTSD).

Introduction

A google search for the term "medicalization" yielded more than 4,50,000 hits. Medicalization is the process by which some aspects of human life, which were not pathological before, begin to be considered as medical problems (1). It has also been defined as "applying a diagnostic label to various unpleasant or undesirable feelings or behaviors that are not distinctly abnormal but fall within a gray area, not readily distinguishable from the range of experiences that are often inescapable

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aspects of the fate of being human" (2).

From a sociological perspective, medicalization comes close to the "iatrogenic concept" (3), a Greek word that means, "Originating from physician or treatment". One of the examples of social iatrogenesis is lowering of tolerance levels for psychological discomfort or sadness that has brought a steady increase in diagnosis of depression (4).

In 2007, Conrad proposed three aspects of medicalization, "Conceptual medicalization" refers to use of medical lexicon to define non-medical entities, for example, natural drooping of breasts after pregnancy diagnosed as mammary ptosis. "Institutional medicalization" refers to physician taking on management roles without having any such experience. And finally, "Interactional medicalization"that occurs when the physician redefines a social problem as a medical one, for example, homosexuality as an illness (5).

Medicalization saw a steady rise after the 1970s. Routine human conditions like unhappiness, bone thinning, stomach aches and boredom were being re-defined as disease. Depression in its milder forms, osteoporosis, irritable bowel syndrome and attention deficit disorder started getting disease labels. Conrad, in 2005, suggested that increase in managerial powers of physicians, role of social activist groups in promoting medical definition of social problems and rise of pharmaceutical industries were important contributors in this rise disease labels (6).

Bio-medicalization was also seen as an important transformation in the field. Clarke and her colleagues defined bio-medicalization as, "the increasingly complex, multi-sited, multidirectional processes of medicalization that today are being reconstituted through the emergent social forms and practices of a highly and increasingly techno-scientific biomedicine" (7). They further postulated that bio-medicalization brought about dramatic changes in organization as well as practice of contemporary medicine.

The three engines of medicalization are often considered to be consumers, technology, and managed care. For lay public or consumers, health has become a commodity and they are increasingly using medical technology in order to understand their health. Second, technology drives medicalization

through development of newer diagnostic tools, which can "discover" illnesses in individuals. Finally, managed care with its provision for reimbursement for some illnesses and treatment, also influenced the movement. For example, considering depression as a medical diagnosis legitimatized use of pills rather than psychotherapy as the former was being covered in managed care (8).

One of the strongest critique of modern medicine or medicalization comes from Illich, who argued that pain, suffering and death are inevitable part of human race and all cultures have always aimed at helping individuals cope with these. He further postulated that modern medicine has destroyed these cultural and individual capacities by attempting to defeat these three (9). AmratyaSen also observed that more a society spends on healthcare, the more sick their members become (10).

Medical Marketing and Medicalization

With advent in managed care, corporatized medicine and rise of biotechnology, medical markets are becoming increasingly important in the healthcare systems. Medical markets develop when medical products, services or treatments are promoted to consumers to improve their health, appearance or general well-being. However, medical markets often differ from traditional, competitive marketplace as they involve asymmetry of information, uncertainity in diagnosis, lack of bargaining power and free choice about buying (11,12).

The Federal Drug Administration (FDA) Modernization Act (1997) loosened the restriction placed on the kind of information pharmaceutical industries could share with prescription, especially regarding "off-label" use of drugs, which further facilitated the process of medicalization (13). The use of advertising has become commonplace and has contributed significantly to increased commodification of services and goods (14). Viagra (sildenafil) to treat male erectile dysfunction and Paxil (paroxetine) to treat social anxiety disorders have made significant contributions in the medicalization of the two diagnosis. GlaxoSmithKline, while marketing paroxetine in the late 1990s, distributed pamphlets suggesting that one in eight Americans had social anxiety disorder, marketing shyness as a disorder that needed attention.

Another aspect of marketing that has promoted medicalization have been the establishment of private markets, which emerge when an available medical intervention finds consumers willing to pay from their pockets. Some of these interventions can be seen as medical enhancement rather than treatment for diseases, but have shaped how these conditions are looked upon. For example, surgery for breast enhancement, use of human growth hormones for idiopathic shortness and in-vitro fertilization for infertility.

Medicalization: Boon or Bane

As with everything, medicalization has a good as well as a dark side. According to Conrad and Schneider, the benefits of medicalization included, "…the creation of humanitarian and non-punitive sanctions; the extension of the sick role to some deviants; a reduction of individual responsibility, blame, and possibly stigma for deviance; an optimistic therapeutic ideology; care and treatment rendered by a prestigious medical profession; and the availability of a more flexible and often more efficient means of social control [than criminalization]"(15).

However, the concept also suffers from various disadvantages like construing non-medical problems as medical problems and viewing normal human variations as pathological. Further, the process of medicalization undermines human beings as subjects, for example, treating criminal behaviour as a part of psychiatric disorder indicates seeing ourselves as subjects under mercy of forces beyond our own self. Also, since the focus shifts to reducing suffering of the individuals, less attention is given to change social conditions that produced those behaviors in the first place (16).

Medicalization in Psychiatry

In nineteenth century, several developments acted as engines that drove medicalization of psychiatry, for example, introduction of medical terminology, process of delineating boundaries between health and pathology, shift of care from family to physician and from community to institution and the changing medically sanctioned nosological status (17).

Over the years, the Diagnostic and Statistical Manual for Mental Disorders (DSM) saw a rapidly increasing number of diagnostic categories (from 106 in DSM-I in 1952 to 357 in DSM-IV in

1994). The increase occurred in the context of making psychiatric diagnosis more reliable. DSM-III encouraged labelling of psychological conditions and conditions such as social phobia and post-traumatic stress disorder (PTSD) were included as disorders. DSM-IV further expanded the list to include impotence, premature ejaculation, jet lag, caffeine intoxication, personality problems, and adult attention deficit as mental illnesses. Moreover, from DSM-I to DSM-IV, there was a significant change in perspective; with the later editions including only broad, observable behaviours to make a diagnosis, while excluding any mention of social etiology and a shift away from Freud's psychoanalytic theory. Similar patterns were observed in the International Statistical Classification of Diseases and Health Related Problems (ICD) classifications. This, combined with introduction of newer medications to treat disorders, led everyday emotional suffering and behaviors to be labelled as mental disorders (18).

An important development in this period was beginning of the movement known as "post-psychiatry", which criticized the monolithic, biological explanations of mental illness. The movement, following the legacy of Friedrich Nietzche, proposed that mental illnesses could be approached from a number of different perspectives and that one analytic frame would not be able to explain the complexity of mental illnesses (19, 20).

Gradually, as the trend towards medicalization increases, more and more people are diagnosed as having a psychiatric illness and needing psychotropic medication. This advent is most alarming in children. A series in the New York Times documented increase in prescription of multiple drugs to children as young as three years for behaviors such as temper tantrums, excitability and disruptiveness (21).

Attention Deficit Hyperactivity Disorder (ADHD) and Medicalization

The dispute over treatment, causes and existence of ADHD has continued for decades. A report by National Institute of Mental Health claimed that ADHD is one of the commonest mental disorders in children and adolescents (22). Earlier believed to be remitted by adolescence, it is now believed to affect even adults.

This increase in the diagnosis of ADHD has paralleled the increase in the prescription of stimulant drugs (23). Many authors claim that behaviors

diagnosed as ADHD are often similar to those displayed by children when they are bored or frustrated. Therefore, the observable deviant behaviour is often a reflection of disciplinary styles in schools and families. For example, epidemiological studies have shown less prevalence of ADHD in Europe where more "traditional authoritarian" style is followed in school as compared to USA where the trend is to follow "medical authoritarianism" (24). Thus, increasing use of ADHD diagnosis and pharmacological ways of treating the same tend to reflect a displacement strategy for the difficult task of improving family and social life.

PTSD and Medicalization

The 1800s saw the beginning of trauma-related nervous disorders, when the soldiers displayed signs of mental shutdown after trauma experience and were diagnosed as having "exhaustion". The condition was first medicalized in 1876 and termed the "soldier's heart" (25). There was little consensus about the etiology and treatment of the condition amongst the clinicians, who found it increasingly difficult to distinguish between legitimate and illegitimate cases. Initially believed to be caused due to psychological weakness in soldiers, it was later realized that disorder still existed even if adequate screening was done during selection of soldiers before wars. Both the world-wars saw huge casualties and the disorder was given various names such as "shell shock", "combat fatigue" etc. By the end of world-war II and Vietnamese war, it was realized that the condition is a real one and severe trauma is the main cause behind it. Thus, in DSM-III, the diagnosis of PTSD was created (26).

Quite a few remain sceptical about the medicalization of trauma and argue that PTSD is a label and a social construct applied to distress for socio-political reasons. It has also been argued that the diagnosis emerged just as an attempt to overcome social crisis of Vietnam and has been influenced by financial incentives (27).

Many others note that in western times, the conflation of distress with trauma has taken a naturalistic feel and trauma has become part of every day's description of life's problems. In an editorial, Andreason noted that unlike other diagnosis, PTSD was one that people liked to have (28). Originally, conceived to be applicable to those who experienced extreme

trauma, medicalization has resulted in it being associated with vast number of experiences ranging from accidents, mugging, verbal sexual harassment, etc. Thus, the diagnosis is criticized for being used in context of other traumas throughout the world (29).

Sexuality and Medicalization

Sexual life and conduct have been under medical scrutiny for the past two centuries when many aspects that were previously seen as "bad" came to be re-framed as "sick"(15). Various treatment strategies like pharmacological, surgical and psychotherapeutic interventions have been developed to deal with sexual issues. Numerous aetiologies have been proposed to understand gender roles, partner preference, paraphilic deviations and sexual drive.

As with other categories, sexual issues have undergone radical changes from DSM I to current nomenclature. DSM I and II saw that sexual deviations like homosexuality, pedophilia, sexual sadism, etc were classified under personality disorders. The nomenclature changed in DSM III with the deviations being classified in category of "psychosexual dysfunctions". The expansion continued in DSM IV with a category comprising of 27 disorders and titled, "sexual and gender identity disorders". Until DSM II, only deviant sexual behaviors were included within psychopathology; however, from DSM III onwards, even disorders of "normal sexuality" emerged. For example, deficiency of sexuality or "low desire" was also considered pathological.

However, sexual medicalization has sparked substantial critiques and the main debatable issues have been pharmaceutical disease mongering following the success of Viagra, rise of surgeries such as "vaginal rejuvenation" or sex-change therapies, proliferation of pharmaceutical contraceptives and hormonal treatments and various reproductive options (30–32).

Managing Medicalization

Medicalization needs to be managed at different levels. The Health Policy Makers can be prompted to renovate the way diseases are defined, which is free of commercial conflict of interest. At the level of consumers, activist groups can prompt for judicious use of medicines. The government can issue a policy statement regarding medicalization and over-medicalization. The government should also undertake

progammes through which citizens can be made aware of the dangers and side-effects of medication. There is a need to challenge the over-diagnosis and over-consumption of medicines and for people to change their lifestyles. Moreover, the medical fraternity should not overlook the personal coping skills of the individuals (33–35).

The mindful thinking of psychiatric physicians should focus on the biological aspects of mental illness. Diagnosis should be made as per the standard diagnostic criteria. Research efforts should be directed further at improving the reliability and validity of diagnosis and classification.

Mental health professionals need to review the definition of the different psychiatric disorders as a disease and decide whether they have sufficient robustness and explanatory power to apply to the diverse uses to which it is now being put. Society confers on doctors the power to award disease status and the social advantages attached to the sick role. Current practice, which labels people as being mentally ill when they are not, calls this public duty of doctors into question.

Conclusion

The concept of medicalization has been present since decades; however, it has seen a steady increase since the 1970s. Mental health issues and medicalization have been one of the most debatable issues as often the boundaries between normal and abnormal are blurred. Some of the diagnosis, which have received particular attention are ADHD that includes both children and adults, PTSD, sexual disorders and social anxiety disorders. Therefore, it is imperative that steps are taken at all levels to counter the effects of medicalization especially in the field of mental health.

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Modulatory Role of Oxytocin during Opioidergic Regulation of Food Intake in Rats

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ABSTRACT

Effects of acute and chronic administration of μ- and k-opioid receptor agonists, morphine (MOR) and ketocyclazocine (KCZ), on food intake and their interaction with neuro-hypophysial neuropeptide, oxytocin (OXY) have been investigated in rats. After single administration of MOR (1 μg/rat, icv) food intake was increased during the light phase (0- 6 h) as well as dark phase (6-24 h) in naïve rats. Similarly, single administration of KCZ enhanced the food intake during the light phase but with not much change in food intake during the dark phase. However, after chronic administration the responses were differentially modified, i.e. there was a further enhancement of hyperphagic effect of MOR during light phase (0-6 h), whereas tolerance developed to orexic effect of KCZ. Further, during dark phase, hyperphagic response was observed in response to both MOR and KCZ. During interaction studies with OXY, it was observed that pretreatment with OXY (0.1 μg/rat, icv) attenuated the hyperphagic response to single administration of both MOR and KCZ. OXY, per se, did not significantly affect the food intake response during light or dark phases of the diurnal cycle. However, on chronic treatment OXY (a) blocked the accentuation of hyperphagic response to MOR during both 0-6 h and 6-24 h and (b) blocked the

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hyperphagic response to KCZ during 6-24 h. Results are discussed in the light of complex opioid-oxytocin interaction during food intake in rats.

Keywords: Morphine, oxytocin, ketocyclazocine, food intake.

Introduction

Feeding or ingestive behavior is one of the many natural instincts possessed by both animals and men aimed at maintaining homeostasis. This is influenced by several cognitive and social factors, modulation in which can result in predictable changes in eating, body weight and energy output. Accordingly, an adequate control system for feeding seems mandatory. Both central and peripheral mechanisms have been implicated in food intake regulation (1-4).

Opioid peptides, initially known for their classical role in the regulation of pain sensitivity are now known to have important functions as mediator of various physiological processes involved in maintenance of bodily homeostasis, viz. cardiovascular responses, temperature regulation, endocrine responses, immune function, emotional responses, feeding control, etc. (5, 6). Being one of the important vegetative functions, the role of opioids in the control of ingestive behavior has been investigated (7, 8). For the first time Martin et al (9) reported stimulated feeding in free-fed rats following daily morphine (MOR) injection. Subsequent studies indicated that chronically administered (sc) MOR, heroin, codeine and levorphanol initially depressed feeding for 1 h, then stimulated it for 6 h. Although opioid antagonists have been constantly shown to produce hypophagia, opioid agonists are reported to produce variable effects, e.g. facilitation of food intake by methadone, MOR and pentazocine have been observed by Grandison and Guidotti (10), while Ostrowski et al (11) reported decreased consumption of food intake in food deprived rats in a dose dependent manner by MOR. However, Jackson and Cooper (12) demonstrated that MOR (0.3-10 mg/kg, ip) had no hyperphagic effect. The preferential k-agonist, ketocyclazocine (KCZ) was found to be more potent stimulators of food intake in rats. Morley et al (13) confirmed the orexic responses to highly specific k-agonist, U50-488H

and stereospecific effect of tifluadom. Contrary to this finding Ramarao and Bhargava (14) failed to demonstrate any effect of U50-488H, bremazocine and tifluadom on food consumption in free-fed rats, whereas in food deprived rats inhibition by bremazocine and facilitation by tifluadom was observed. They suggested that the differential responses may be related to either the existence of more than one population of receptors or their differential actions at opioid receptor type. Gulati et al (15, 16) demonstrated receptor-specific regulation of food intake by MOR and KCZ which is governed by diurnal variation and fasting status of rats. Similar modulation in food intake was observed after peripheral, icv or intrahypothalamic administration of MOR and KCZ in naïve and tolerant rats, suggesting central opioidergic regulation of the ingestive behavior with differential involvement of μ- or k-receptors (17-20). Demonstration of several endopioidergic receptors and their interactions with other neuropeptides lend further complexity to the picture as far as regulation of food intake is concerned.

Opioid peptides are known to interact with several neurotransmitters including some neuropeptides during the expression of several centrally mediated behavioral paradigms. A number of studies have suggested complex interactions between opioids and oxytocin (OXY) and arginine-vasopressin (AVP), the two neurohypophyseal peptides which are found in the hypothalamus (21-24). Endogenous opioids, enkephalin and dynorphin have been shown to colocalize with OXY and AVP, respectively in the same neurons in the paraventricular and supraoptic nucleus and regulate each other's release (25). Moreover, OXY is reported to inhibit the development of tolerance to the analgesic effects of MOR, βendorphin, etc and AVP facilitates the rate of this tolerance development (21). However, no reports are available regarding such opioid-OXY interactions during ingestive behavior (21, 26, 27). The present work was thus designed to explore any possible opioid-OXY interactions during food intake in rats. Further since the physiological role of μ- and βreceptors are clearly delineated in other behaviors like antinociception, respiratory depression, cardiovascular control and euphoria, the effects of μ- and βdirected drugs were evaluated in such interactions during food intake.

Materials and methods

Male Wistar rats (200-250g) maintained under standard laboratory conditions of dark and light cycle of 18 h dark and 6 h light was used. Rats were housed individually and randomly allocated to four groups of 7 rats each and were given food ad libitum. For surgery, rats were anesthetized with pentobarbitone sodium (35 mg/kg ip) and secured in stereotaxic apparatus. Twenty three gauge stainless steel guide cannulae were placed into lateral ventricle using following coordinates: 1.5P (to bregma), 2L (to midline) and 4V (to dura), skull horizontal. The cannulae were secured in position and anchored to the skull by steel screws and dental acrylic. Oozing out of cerebrospinal fluid from the outer tip of cannula certified its placement in the lateral ventricle. After one week of postoperative recovery period and stabilization of basal food intake, they were administered icv vehicle, MOR (1µg/rat; Govt. Narcotics Lab, Ghazipur), OXY (0.1µg/rat; Sigma), OXY + MOR in separate groups. After 15 minutes of administration of vehicle or drugs, preweighed food pellets (Hindustan Lever, Bombay) were placed in the cage and quantity of food consumed was measured at 1, 3,6 (0-6 h light phase) and 6-24 h (dark phase) after commencing the experiment. All significant spillage was collected and deducted from the amount consumed. After completion of the acute study, the respective groups of animals were continued for seven days with saline or escalating doses of MOR (5 to 35 mg/kg, ip twice a day with an increment of 5 mg/kg/day). In the OXY interaction studies, the peptide was injected prior to each dose of MOR during the seven days treatment schedule. This was followed by a withdrawal period of 36 h. Food intake in response to test dose of MOR (1µg/rat, icv) was measured in these tolerant rats as was measured for naïve rats after single administration of MOR.

A similar set of experiments was done to study OXY (0.1µg/rat) and KCZ (1µg/rat, icv, Sterling Winthrop, Rensselaer, NY) interactions. For chronic studies, escalating doses of KCZ from 1 to 8 mg/kg, ip twice daily at 0900 and 1500 h were administered. The dose was doubled every third day upto eighth day. Food intake in response to test dose of KCZ (1 µg/rat) was measured on first and eighth day after 36 h of withdrawal period. All drugs were dissolved in saline, except KCZ which was dissolved

in 0.1 N HCl and then diluted with saline.

The data were analyzed by ANOVA followed by Student's paired 't' test to compare the food intake responses after acute and chronic drug administration. Post hoc Tukey's test was applied to compare drugs treated groups. A 'p' value of at least 0.05 was considered as the level of significance in all statistical tests.

Results

Acute treatment with MOR (1μg/rat, icv) resulted in a significant enhancement of cumulative food intake for 6 h ($p < 0.05$) as compared to vehicle treated group, the most remarkable increase being during 0-1 h, i.e. a 98% increase in food intake was observed (Table 1). Overall, for 0-6 h (light phase of the day) there was an increase in food intake by 23% from that observed in vehicle treated group. Prior treatment with naltrexone (5 μg/rat, icv) significantly blocked the hyperphagic response to MOR during all the time intervals (data not shown). Thus, suggesting that the response is specifically mediated through μ-receptors. After chronic administration with escalating doses of MOR, the test dose produced a significant accentuation of hyperphagic response during 0-1 h; the hyperphagic response was increased to 148% vs 98% in naïve rats. Overall for 0-6 h, there was an increase in food intake by 91% in tolerant rats compared to 23% in naïve rats (Table 1). OXY per se reduced the food intake only marginally, i.e. by 11% as compared to saline treated animals during 0-6 h and 6-24 h (Table 1). However, this did not attain level of statistical significance after both acute as well as chronic administration. There was no appreciable difference between reduction in food intake after single or repeated exposure to OXY. Pretreatment with OXY reduced the hyperphagic effect of single injection of MOR by approximately 10% during 0-6 h and 20% during 6-24 h. Chronic treatment with (central) OXY along with peripheral MOR significantly blocked the accentuation of hyperphagic response of 91% ($p < 0.05$) observed in animals treated with MOR alone was reduced to 25% in OXY+MOR group. Similarly, the 6-24 h (dark phase) food intake was also reduced significantly.

Acute administration of KCZ significantly enhanced food intake during all the time intervals, i.e. 0-1, 3-6 and 0-6 h during light phase ($p < 0.05$, Table 2), but it was not increased during dark phase. Pretreatment with βreceptor antagonist,

Table 1: Effects of morphine (MOR, 1 µg/rat, icv) and oxytocin (OXY, 0.1 µg/rat, icv) on food intake in naive and tolerant rats.

Treatment	n	Food intake (g) ± SE									
		0-1 h		1-3 h		3-6 h		0-6 h		6-24 h	
		Naive	Tolerant	Naïve	Tolerant	Naive	Tolerant	Naive	Tolerant	Naive	Tolerant
Vehicle	7	2.04±0.28	2.74±0.21	1.76±0.28	2.36±0.26	2.14±0.29	1.17±0.14	5.94±0.45	6.27±0.27	13.34±0.69	12.71±0.94
MOR	7	4.03±0.77 *	6.80±0.62 *#	2.20±0.12	2.85±0.40	1.42±0.16	2.35±0.20 *	7.30±0.59 *	12.00±0.79 *#	18.50±0.92*	15.65±0.82*
OXY	7	2.92±0.17	2.72±0.26	1.25±0.12 *	1.42±0.18	1.13±0.25	2.37±0.24	5.30±0.27	6.50±0.50	11.80±0.75	13.68±1.04
OXY+ MOR	7	3.28±0.38	4.83±0.37	2.20±0.10	1.63±0.16#	1.27±0.14	1.77±0.55	6.75±0.47	7.82±0.55	14.60±1.13	10.03±0.80

* P < 0.05 compare to respective vehicle treated group; # P < 0.05 compared to respective naïve group

Table 2: Effects of ketocyclazocine (KCZ, 1 µg/rat, icv) and oxytocin (OXY, 0.1 µg/rat, icv) on food intake in naive and tolerant rats.

Treatment	n	Food intake (g) ± SE									
		0-1 h		1-3 h		3-6 h		0-6 h		6-24 h	
		Naive	Tolerant	Naïve	Tolerant	Naive	Tolerant	Naive	Tolerant	Naive	Tolerant
Vehicle	7	2.06±0.29	2.34±0.36	2.50±0.38	2.38±0.33	2.08±0.36	1.84±0.28	6.64±0.92	6.56±0.65	13.00±1.41	14.10±0.78
KCZ	7	3.70±0.30 *	1.95±0.24 #	2.38±0.24	2.41±0.17	3.73±0.40 *	1.49±0.28 #	9.80±0.78 *	5.85±0.37 #	16.30±1.32	19.60±1.02*
OXY	7	1.53±0.42	2.05±0.17	1.88±0.17	2.25±0.16	2.95±0.44	3.30±0.28	5.47±0.36	6.60±0.24	12.28±0.79	14.30±0.88
OXY+ KCZ	7	2.47±0.40	2.15±0.37	2.37±0.26	1.35±0.21	2.92±0.38	2.58±0.28	7.75±0.59	7.08±0.50	15.48±1.06	17.30±1.21

* P < 0.05 compare to respective vehicle treated group; # P < 0.05 compared to respective naïve group

Mr2266 (0.003 μg/rat, icv) significantly blocked the hyperphagic response (0-6 h) to KCZ (data not shown). After chronic administration, unlike MOR, the light phase-hyperphagic response to KCZ was significantly reduced as compared to that of naïve rats, i.e. tolerance developed to this effect ($p < 0.05$, Table 2). However, there was an accentuation in food intake during 6-24 h, i.e. reverse tolerance was observed. Prior administration of OXY reduced the hyperphagic response to KCZ by 41% as compared to KCZ alone group. Chronic treatment with OXY further attenuated the hyperphagic response to KCZ, i.e. facilitated the development of tolerance during the light phase and blocked hyperphagic response during the dark phase (Table 2).

Discussion

The results of the present study showed that icv administration of μ- as well as β receptor agonists, MOR and KCZ, respectively enhanced food intake during light phase (0-6 h). The involvement of specific μ - and β receptors in this hyperphagic effect is evident from blockade of the response by respective antagonists, naltrexone and Mr2266 (data not shown). These findings are in line with those suggesting role of both μ- and β receptors in ingestive behavior (12, 28).

Interestingly, after repeated administration with MOR the test dose of MOR markedly enhanced the hyperphagic response during 0-6 h as compared to that after acute injection. The observation of lack of tolerance to this effect is in contrast to the analgesic response and is similar to that of lowering of self-stimulation-threshold following chronic administration of opiate agonists (29). In fact, Morley et al (12) also reported similar enhancement of food intake following repeated injections of opioids and termed it as 'reverse tolerance'. It may be due to different type/subtypes of opioid receptors and central sites involved in feeding behavior from those involved in analgesia.This is supported by the fact that no correlation was found between antagonists' potency in reducing eating and blocking analgesia (30, 31). Alternatively, it could be due to sensitization of receptors mediating excitatory responses after chronic administration (29).

The present results clearly show that the βagonist, KCZ produces differential effects on food intake after acute and

chronic administration. KCZ lead to increased food intake during 0-6 h with not much change during 6-24 h. After repeated administration of KCZ tolerance developed to the acute hyperphagic effect during the light phase (0-6 h). This could be due to reduced levels of endogenous β-ligand as β-agonists are known to act on autoreceptors and inhibit the release of dynorphin which has definite role in enhancing food intake (32). However, an increase in food intake was observed during 6-24 h as compared to that in naïve rats. The facilitation in the dark phase (6-24 h) food intake after chronic KCZ administration is interesting and some reports have termed such a trend as "reverse tolerance" as has been with MOR in the present and earlier studies (7, 13).

The differential temporal adaptive changes in food intake in response to chronic administration of KCZ and MOR may be due to the diurnal variation in the levels of endogenous μ- and β-directed ligands. Moreover, Bhargava et al (33) also demonstrated an up-regulation of brain and spinal cord β opioid receptors in rats with downregulated μ-receptors following repeated treatment with MOR.

These feeding inhibitory effects of OXY on both the μ- and k-opioid agonists, MOR and KCZ get credence from the results of Olszewski et al (34) who also observed an inhibition of food consumatory behaviour by OXY. Anorexic effect of OXY also get support from studies where OXY-null mice were observed to ingest enhanced amount of sweet solution during both light and dark cycles of the day (35) and clinical findings of hyperphagia and morbid obesity reported in patients of Prader-Willi syndrome who (besides showing mild mental retardation, short stature, abnormal body composition, muscular hypotonia, and distinctive behavioural features) also exhibit low levels of OXY, growth hormone, insulin and insulin-like growth factor alongwith hyperghrelinaemia (36).

Neuropeptides are reported to interact with each other during expression of several centrally mediated behavioral paradigms (21-25, 37). The hypothalamus, which is crucial for physiological regulation of food intake, is rich in both opioidergic and oxytocinergic nerve terminals. Further, colocalization of endogenous opioids and OXY in the same terminal is also

reported, suggesting that the regulation of the release/effect of one by the other is possible (37). Our results show that OXY is effective in attenuating MOR-induced food intake responses during the light and dark phases after both acute and chronic administration. Another notable aspect of our study is the complex interactions of KCZ with OXY during feeding behavior. The (acute) hyperphagic effect of KCZ during the light phase (0-6 h) is markedly attenuated by OXY. In addition this neurohypophyseal peptide prevented the tolerance development to the acute effects of KCZ. Further, both endogenous opioids and neurohypophyseal peptides are known to interact with classical neurotransmitters like NA, DA, 5-HT, etc. (38-42), and the net outcome of such interactions could have contributed to the present results. The probable mechanism of such interaction is hard to define on the basis of the present data. Nevertheless, the concept of such an interaction may be of some physiological significance particularly because both groups of neuropeptides are found in those areas of the CNS, like hypothalamus, amygdale, etc., which are seemingly crucial for feeding behavior.

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